Title: Monitoring pulmonary health in Swiss childhood cancer survivors

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Abbreviations:

CCS	Childhood cancer survivors
CNS	Central nervous system
CI	Confidence interval
CuI	Cumulative incidence
DLCO	Diffusion capacity of the lung for carbon monoxide
Gy	Gray
HSCT	Hematopoietic stem cell transplantation
ICCC-3	International Classification of Childhood Cancer, Third edition
IQR	Interquartile range
MBW	Multiple breath washout
OR	Odds ratio
PFT	Pulmonary function tests
SCCR	Swiss Childhood Cancer Registry

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Abstract

Background:

Childhood cancer survivors are at increased risk for pulmonary morbidity and mortality. International guidelines recommend pulmonary function tests (PFT) during follow-up care. This nationwide study assessed how many children received PFT within five years after pulmotoxic treatment in Switzerland, types of tests, and predictors for testing.

Methods:

We included all children from the Swiss Childhood Cancer Registry who were diagnosed with cancer from 1990-2013 at age 0-16 years, survived for ≥2 years from diagnosis and had pulmotoxic chemotherapy with bleomycin, busulfan, nitrosoureas and/or chest radiotherapy. We searched medical records in all Swiss pediatric oncology clinics for PFT (spirometry, plethysmography, diffusion capacity of carbon monoxide [DLCO]) and treatment details.

Results:

We found medical records for 372 children, of whom 147 had pulmotoxic chemotherapy and 323 chest radiotherapy. Only 185 had plethysmography and/or spirometry (50%), 122 had DLCO (33%). Testing varied by cancer center from 3% to 79% (p=0.001). Central nervous system tumor survivors and those not treated according to study protocols had less plethysmography and/or spirometry (odds ratio (OR): 0.3 and 0.3), lymphoma survivors and those who were symptomatic had more PFTs (plethysmography and/or spirometry: OR: 5.9 and 8.7; DLCO: OR: 3.4 and 2.3). Cumulative incidence of PFT (CuI) was 52% in the first five years after pulmotoxic treatment; most of the tests were done in the first two years after treatment (CuI 44%).

Conclusion:

Only half of survivors exposed to pulmotoxic treatment have been followed up with PFT in Switzerland. We need to optimize, update, and implement monitoring guidelines.

Introduction

Every fifth childhood cancer survivor (CCS) is exposed to pulmotoxic cancer treatment with either bleomycin, busulfan, nitrosoureas and/or radiotherapy involving lung tissue.[1] These treatments can lead to lung damage and pulmonary diseases that are a major cause of mortality and morbidity in CCS. CCS have a three-fold increased risk of hospitalization due to pulmonary diseases and up to 14 times increased risk of late pulmonary death.[2-4] In Switzerland, 12% of CCS report one or more pulmonary diseases, possibly caused by cancer treatment.[1] In the St. Jude Lifetime Cohort, in which all CCS received risk-based screening at a median of 25 years after cancer treatment, 65% of 417 CCS exposed to pulmotoxic treatment had abnormal pulmonary function tests (PFT).[5] Prior to testing, more than half were unaware of their pulmonary dysfunction, which was the most frequently detected adverse health effect.[5] A similar study performed in 370 CCS from the City of Hope Hospital also found that the yield of screening for pulmonary dysfunction was higher (84%) than for other late effects including hearing loss (23%), low bone mineral density (23%) or hypothyroidism (11%).[6]

Early detection of pulmonary dysfunction can help guide treatment and inform lifestyle modifications to mitigate progression and reduce exacerbation.[7] Since 1995 international follow-up care guidelines in the UK and since 2003 in the US have therefore recommended PFT for CCS at risk of pulmonary dysfunction.[8,9] Switzerland has no national guidelines, and routine practice of PFT in follow-up care after childhood cancer is unknown.

In this national, population-based study we retrospectively studied three aspects of pulmonary function testing during follow-up care of CCS in Switzerland: the type of

PFT performed, how many CCS were tested, and the characteristics of CCS who had had PFT compared to those who had not.

Methods

Study population

This study is a nested cohort in the Swiss Childhood Cancer Registry (SCCR). The SCCR includes all children and adolescents who live in Switzerland and are diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis prior to the age of 21 years.[10] The SCCR is a national, population-based registry that includes more than 95% of childhood cancer patients diagnosed since 1995.[11] It registers information on cancer diagnosis and treatment, and personal information. Tumors are classified according to the International Classification of Childhood Cancer, third edition (ICCC-3).[12] Ethics approval was granted by the Ethics Committee of the Canton of Bern to the SCCR (KEK-BE: 166/2014).

Inclusion criteria

We included all CCS registered in the SCCR who were treated with pulmotoxic chemotherapy and/or chest radiotherapy in a Swiss pediatric oncology center up to the age of 16 years and aged ≥6 years at time of the study (Supplementary Fig. S1). We defined pulmotoxic chemotherapy as treatment with busulfan, bleomycin, and/or nitrosoureas (lomustine, carmustine) according to international follow-up care guidelines (Supplementary Table S1).[8,9] Radiotherapy relevant for this study was defined as any

radiation applied to the whole body, mantle-field, chest, lungs, mediastinum or thoracic spine.[8,9] We included CCS diagnosed from 1990 to 2013. According to Swiss law, medical records need to be stored for only 10-20 years so we excluded those CCS diagnosed before 1990 to preserve completeness of data.[13] We excluded CCS diagnosed after 2013 because treatment was not always completed when data collection started in 2016.

Medical records review

For this retrospective data collection, we accessed medical records in 2016 in all Swiss pediatric oncology centers and the corresponding pediatric respiratory clinics. We collected PFT, reports of pediatric pulmonologists, reports of ambulatory oncology care, hospitalization discharge reports, and cancer treatment protocols.

Switzerland has no national recommendations on type and timing of PFT in CCS after pulmotoxic treatment. We therefore decided on a simplified approach and collected all PFT performed in the first five years after pulmotoxic treatment regardless of the reasons for performing the tests. We collected information on all tests specifically recommended for assessment of pulmonary late effects by international guidelines, i.e. spirometry, plethysmography and diffusion capacity of carbon monoxide (DLCO),[8,9] and also noted other tests performed including bronchodilator tests, cardiopulmonary exercise tests, measurement of exhaled nitric oxide, bronchial challenge test, and multiple breath inert gas washout. We reviewed medical reports from pulmonologists and pediatric oncology for pulmonary diagnoses, distinguishing between noninfectious pulmonary diseases and pulmonary infections. Noninfectious pulmonary diseases found

in the medical records were asthma, diffuse parenchymal lung disease (restrictive lung disease, interstitial lung disease, bronchiolitis obliterans), atelectasis, chest wall deformity, emphysema, and acute respiratory distress syndrome (ARDS). Infections listed in the records were viral or bacterial pneumonia and aspergillosis. CCS who had both noninfectious pulmonary disease and infection, were classified as having noninfectious pulmonary disease, which we considered more permanent.

We collected detailed information on cancer treatment from the SCCR or, when it was not available in the SCCR, medical records, recording the start date of pulmotoxic treatment. We classified CCS into three groups depending on the pulmotoxic treatment: chest radiotherapy, pulmotoxic chemotherapy, or both. We determined whether CCS were registered clinical study participants, were treated according to a clinical study protocol but not registered, or were not treated according to a clinical study protocol. If children received multiple pulmotoxic treatments (e.g. for primary tumor and relapse) the last treatment was the one used in categorization of clinical study participation. We recorded information on thoracic surgery with thoracotomy or thoracoscopy for tumor/metastasis resection (wedge, lobe, whole lung), rib resection, laminectomy, bone biopsy, en bloc resection of rib, lung tissue, and/or diaphragm. We recorded autologous or allogeneic hematopoietic stem cell transplantation (HSCT). We also collected information on relapse of the cancer and survival.

Statistical analysis

We assessed the proportion of CCS who had different types of PFT during the first 5 years after pulmotoxic treatment. Among those who had been tested, we

calculated the median number, interquartile range, and range of PFT. We stratified the results by sex, age at diagnosis, diagnosis, period of cancer diagnosis, pulmotoxic treatment, thoracic surgery, HSCT, clinical study participation, pulmonary disease diagnosis, or death during follow-up care and assessed associations using univariable and multivariable logistic regression models. In a sensitivity analysis we excluded all children with asthma (19 children) from the model, because we suspected that children with asthma would receive PFT to assess asthma control rather than screen for sequelae of cancer treatment. Finally, we used the Kaplan-Meier method to estimate cumulative incidence curves for PFT performed during the first five years after pulmotoxic treatment overall, and stratified by period of cancer diagnosis. CCS who had not had a PFT were censored at five years of follow-up, death, or start of data collection (February 2, 2016), whichever occurred first. In eight cases in which we had no information on the start of pulmotoxic treatment, we considered the start date to be the date of the cancer diagnosis.

We used Stata (Version 14, Stata Corporation, Austin, Texas) for all analyses.

Results

Characteristics of study population

Of 2989 eligible CCS, 419 (14%) received pulmotoxic treatment and were at least six years old at start of data collection. Medical records were unavailable in 47 of those CCS (Supplementary Fig. S1). Table 1 lists the characteristics of the 372 CCS included in the analysis, 147 of whom had received pulmotoxic chemotherapy (40%), while 324 received chest radiotherapy (87%). Pulmonary diseases were present in 72

CCS, of whom 47 had noninfectious pulmonary disease and 25 pulmonary infections (Supplementary Table S2).

Pulmonary function tests

Within five years after pulmotoxic treatment, 185 of 372 CCS (50%) had received at least one PFT. All 185 CCS in whom pulmonary function had been tested had at least a spirometry and/or body plethysmography; the median number of plethysmography and/or spirometry tests per tested child was 3 (IQR 2–5). DLCO was done at least once in 122 CCS (33%), and the median number of DLCO per tested child was 3 (IQR 2–4). Other tests performed were bronchodilator tests, cardiopulmonary exercise tests, fractionated exhaled nitric oxide, bronchial challenge tests, and multiple breath inert gas washout (Table 2).

Predictors for pulmonary function tests

Testing varied strongly by cancer treatment centers: center A was clearly above average and had done both plethysmography and/or spirometry and DLCO in 79% of children. All other centers did plethysmography and/or spirometry in 26% to 58%, and DLCO in 3% to 44% (Fig. 1, Supplementary Table S3). Children who were older at diagnosis were more often tested (had higher odds for being tested) than those younger at diagnosis, although age at diagnosis was not statistically significant after adjustment (Table 3, Supplementary Table S4). Compared to patients with leukemia, survivors of lymphoma were tested more often (odds ratio (OR) 5.9 for plethysmography and spirometry, OR 3.4 for DLCO). CNS tumor survivors were tested less often with

plethysmography and spirometry (OR 0.3), and we observed a tendency for less DLCO measurements, although statistically not significant (OR 0.5). Pulmonary function was tested equally often in children registered as a clinical study participant and those treated according to a study protocol, but those not treated according to a study protocol had less often plethysmographies and/or spirometries (OR 0.3). CCS diagnosed with a noninfectious pulmonary disease were tested much more often than those without pulmonary diseases or pulmonary infections (plethysmography and spirometry OR 8.7, DLCO OR 2.3).

We observed no differences by gender, period of cancer diagnosis, pulmotoxic treatments, thoracic surgery and HSCT (Table 3). In a sensitivity analysis in which we excluded all patients with asthma, results were essentially the same.

Cumulative incidence of pulmonary function tests

The cumulative incidence of children who had a PFT was 31% one year after pulmotoxic treatment, 44% after two years, 48% after three years, 51% after four years, and 52% after five years. Cumulative incidence did not differ between periods of cancer diagnosis (Fig. 2).

Discussion

In our nationwide study of all children who were diagnosed with cancer and exposed to pulmotoxic treatment in Switzerland between 1990 and 2013, we found that only half had PFT during follow-up care. This contrasts sharply with international recommendations (Supplementary Table S1).[8,9] Only 50% of children had a plethysmography and/or spirometry, and only 33% a DLCO. This did not depend on

type of pulmotoxic treatment, but varied significantly between treatment centers and test, from 3% to 79%. Lymphoma survivors and those diagnosed with a non-infectious pulmonary disease were most likely to be tested, while CNS tumor survivors and those not treated according to a study protocol were least likely tested. Most children had the first test within 2 years after pulmotoxic treatment.

Guidelines for PFT in follow-up care differ for type of test and timing. US follow-up care guidelines recommend performing a PFT at entry into long-term follow-up which is defined as “two or more years after completion of therapy” in children exposed to pulmotoxic chemotherapy and/or chest radiotherapy, and thereafter as clinically indicated.[9] They recommend performing a spirometry and a DLCO. UK follow-up care guidelines recommend PFT in exposed children at the end of treatment without further specifying the type of test. In children with symptoms or an abnormal first PFT, the test should be repeated after one year.[8]

In single centers like St. Jude Children’s Research Hospital and City of Hope in the US, follow-up care guidelines are implemented among CCS enrolled in life-time cohorts or long term follow-up clinics.[5,6] For the St. Jude life-time cohort 2843 (60%) of survivors participated in long-term follow-up. Among those, all ten-year survivors with pulmotoxic exposure (n=417, 100%) were screened according to their follow-up guidelines.[5] However, no previous study has investigated PFT in follow-up care on a national level, and in our study we found that only 50% of the children had had PFT. We have reports from single centers in Europe as well, where pulmonary function outcomes in CCS have been studied retrospectively. In a Dutch study, 193 of 220 (88%) CCS exposed to pulmotoxic treatment had a PFT. This is more than in Switzerland, but less

than optimal, considering that the center observes follow-up care guidelines from the US.[14] In an Israeli study of 170 survivors of HSCT, only 34% had had PFT according to their hospital internal protocol.[15] This study cannot be compared directly to ours as the Israeli protocol was stricter and required more tests, including PFT before HSCT, and at 3, 6, and 12 months post-HSCT. No study has investigated in detail which PFT were done in children exposed to pulmotoxic treatments. In our study, DLCO was measured in only 33% of children, which is surprising, since it is a sensitive measure for detecting mild or preclinical interstitial lung disease and helps distinguish interstitial lung disease from extra-pulmonary causes of restriction.[16] Moreover, it is noninvasive, cheap, and needs little time. Also, multiple breath inert gas washout, which measures lung clearance index, was rarely used, although it is sensitive for detection of early small airway disease. Four of the eight pediatric cancer treatment centers had the setup to perform such measurements by 2016 and obviously did not use it for screening of CCS, but mainly for patients with other lung diseases such as cystic fibrosis and for research rather than clinical purposes.[17,18]

The most important predictor for pulmonary function testing was the treatment center, with proportions varying from 24% to 79% for plethysmography and/or spirometry and 3% to 44% for DLCO. This did not depend on the size of the center. We observed the highest proportion in a smaller center with only 28 exposed CCS. This center always performed DLCO together with plethysmography and/or spirometry in CCS. All other centers tested DLCO only in some of the children who had spirometry and/or plethysmography; in three centers the frequency was very low (≤6%). This indicates that centers have different practices of follow-up care or possibly do not follow

any guidelines and, in general have different algorithms for performing PFT. Children diagnosed with a noninfectious pulmonary disease had more PFT than those without. PFT might not have been planned as part of follow-up care but may have been prescribed in response to symptoms. Children with pneumonia or aspergillosis did not have more PFT. This reflects clinical management in which pulmonary infections are not investigated primarily with pulmonary function tests, but rather blood sampling and imaging. CNS tumor survivors were tested the least often. Most CNS tumor survivors, 95 of 107 (89%), received craniospinal radiotherapy, 63 (59%) received nitrosoureas (Supplementary Table S5). The existing follow-up care guidelines all recommend follow-up care for nitrosoureas, but disagree on craniospinal radiotherapy: UK guidelines recommend PFT, while US guidelines do not.[8,9] When we excluded CCS with craniospinal irradiation from the regression and found that CNS tumor survivors still had less pulmonary function tests compared to leukemia survivors. An explanation might be that survivors of CNS tumors often have multiple morbidities, which can shift the attention of clinicians away from the lung.[19] Clinicians might have skipped PFT because they thought that other tests might be more important, or the children were regarded as unable to perform PFT.

Children treated for lymphomas were tested most often. Lymphomas have the best survival rates among all childhood cancers.[20] Late effects after lymphoma are well studied and physicians' awareness for pulmonary late effects is clearly highest.[21,22] This might also have been influenced by the historically more extensive radiation fields involving parts of the lungs g to a study protocol had less PFT. Children cannot be treated according to a protocol when there is no study protocol for their specific disease,

or they fail to meet inclusion criteria of existing protocols. Although this situation can complicate cancer treatment during the acute phase, it should not stop physicians' from doing PFT during follow-up visits. CCS who were treated according to a study protocol had the same likelihood of receiving PFT as those children registered as study participants. Some study protocols containing pulmotoxic treatment have follow-up care recommendations for PFT, and physicians seem to follow such recommendations regardless of whether children are registered participants about half time. However, not all study protocols recommend PFT after pulmotoxic therapy; the HIT-2000 protocol, for example does not do so (Supplementary Table S1). In our study, the proportion of children tested did not depend on the type of pulmotoxic treatment the children had received. Even CCS with a combination of pulmotoxic chemotherapy and radiotherapy were not tested more often. The two international guidelines that are best known to Swiss oncologists were published after 1995 (UK 1995, US 2003).[8,9] Yet, our data do not suggest these guidelines have been implemented in Swiss clinics, since the numbers of tests did not increase after publication of the respective guidelines.

The study was a retrospective chart review in the Swiss pediatric oncology centers. If PFT was done in private practice or other clinics without reporting results, our search would have missed them. But this scenario is unlikely as nearly all CCS are seen in follow-up by their cancer center during the first five years. Spirometry, plethysmography, and DLCO are available in all centers and would have been done there. We did not investigate whether a first PFT was performed later than five years after diagnosis as long term follow up guidelines recommend the initiation either at the end of cancer treatment (UK),[8] or two or more years after completion of therapy (US).[9] However, our

study is likely to have overestimated the adherence to guidelines because we had no detailed information on the indication for PFT. We hypothesized that pulmonary function tests are done often because survivors have symptoms or already diagnosed pulmonary disease rather than because physicians follow international monitoring recommendations on risk based screening. We used presence of pulmonary disease as surrogate for symptoms or diagnosed pulmonary disease before testing. Our analysis supported our initial hypothesis and found that having a symptomatic pulmonary disease is the strongest predictor for having PFTs during follow-up care.

Some guidelines and study protocols recommend imaging such as chest x-ray or computer tomography, but we did not collect this information, because in some clinics access to radiology departments was difficult. Finally, for some participants chemotherapy doses could not be found because in certain older records not all treatment information was available. In such cases we could only confirm whether CCS had chemotherapy.

The strengths of our study include the nationwide, population-based setting. We had original information from medical records to investigate lung health monitoring; we were able to include CCS with different childhood cancer diagnoses and different treatment protocols. Having exact dates of pulmotoxic treatment and PFT made it possible to analyze the timing of monitoring in detail. We also considered children diagnosed over an extended period (1990-2013), which allowed us to evaluate potential changes over the last 23 years.

Surveillance of pulmonary disease is insufficient in Switzerland, particularly for CNS tumor survivors and those not treated according to study protocols in particular are

monitored very rarely. The lack of national monitoring guidelines might have contributed to insufficient surveillance of pulmonary health. The proportions of PFT performed in Swiss centers also vary widely across the centers. Physicians should therefore be surveyed to explore which monitoring guidelines they know and follow, the reasons why they schedule PFT, and why CNS tumor survivors are neglected. Clinicians' knowledge of the importance of pulmonary monitoring after cancer treatment needs to improve.

We observed further that existing guidelines are inconsistent.[8,9] Physician compliance might improve were guidelines harmonized. The need for standardized guidelines for follow-up care was recognized by oncologists and general practitioners in adult and pediatric care in a recent study among Swiss physicians.[23] The International Late Effects of Childhood Cancer Guideline Harmonization Group (www.ighg.org) is currently developing recommendations for pulmonary disease surveillance after cancer treatment to harmonize existing recommendations.[24] The new guidelines, based on current literature, existing guidelines, and broad expert consensus, will propose recommendations about who needs monitoring at what frequency, for how long, and the modalities that should be used (e.g., which PFT, or imaging). Upon publication, these guidelines should be adapted to local needs of different countries and then implemented to offer high quality follow-up care to all former cancer patients.

Conflict of Interest statement

None of the authors report any conflict of interest related to the study.

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References

1. Kasteler R, Weiss A, Schindler M, et al. Long-term pulmonary disease among Swiss childhood cancer survivors. *Pediatric blood & cancer.* Jan 2018;65(1).
2. Lorenzi MF, Xie L, Rogers PC, Pritchard S, Goddard K, McBride ML. Hospital-related morbidity among childhood cancer survivors in British Columbia, Canada: report of the childhood, adolescent, young adult cancer survivors (CAYACS) program. *International journal of cancer. Journal international du cancer.* Apr 01 2011;128(7):1624-1631.
3. Schindler M, Spycher BD, Ammann RA, et al. Cause-specific long-term mortality in survivors of childhood cancer in Switzerland: A population-based study. *International journal of cancer. Journal international du cancer.* Jul 15 2016;139(2):322-333.
4. Reulen RC, Winter DL, Frobisher C, et al. Long-term cause-specific mortality among survivors of childhood cancer. *Jama.* Jul 14 2010;304(2):172-179.
5. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *Jama.* Jun 12 2013;309(22):2371-2381.
6. Landier W, Armenian SH, Lee J, et al. Yield of screening for long-term complications using the children's oncology group long-term follow-up guidelines. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Dec 10 2012;30(35):4401-4408.
7. Versluys AB, Bresters D. Pulmonary complications of childhood cancer treatment. *Paediatric respiratory reviews.* Jan 2016;17:63-70.
8. Skinner R, Wallace WHB, Levitt GA. Therapy based long term follow up: practice statement 2nd edition. 2005. https://www.uhb.nhs.uk/Downloads/pdf/CancerPbTherapyBasedLongTermFollowUp.pdf. Accessed 02 Feb 2018.
9. Childrens oncology group (COG). COG Long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancer, version 4.0. 2013. http://www.survivorshipguidelines.org/. Accessed 02 Feb 2018.
10. Michel G, von der Weid NX, Zwahlen M, Adam M, Rebholz CE, Kuehni CE. The Swiss Childhood Cancer Registry: rationale, organisation and results for the years 2001-2005. *Swiss medical weekly.* Sep 8 2007;137(35-36):502-509.
11. Schindler M, Mitter V, Bergstraesser E, et al. Death certificate notifications in the Swiss Childhood Cancer Registry: assessing completeness and registration procedures. *Swiss medical weekly.* 2015;145:w14225.
12. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer.* Apr 1 2005;103(7):1457-1467.
13. Eidgenössischer Datenschutz- und Öffentlichkeitsbeauftragter (EDÖB). Leitfaden für die Bearbeitung von Personendaten im medizinischen Bereich. Eidgenössischer Datenschutz- und Öffentlichkeitsbeauftragter (EDÖB); 2002. https://www.edoeb.admin.ch/edoeb/de/home/datenschutz/gesundheit.html. Accessed 02 Feb 2018.
14. Mulder RL, Thonissen NM, van der Pal HJ, et al. Pulmonary function impairment measured by pulmonary function tests in long-term survivors of childhood cancer. *Thorax.* Dec 2011;66(12):1065-1071.

15. Prais D, Sinik MM, Stein J, et al. Effectiveness of long-term routine pulmonary function surveillance following pediatric hematopoietic stem cell transplantation. *Pediatric pulmonology.* Nov 2014;49(11):1124-1132.
16. West JB, West JB. *Pulmonary pathophysiology : the essentials.* 8th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2012.
17. Singer F, Kieninger E, Abbas C, et al. Practicability of nitrogen multiple-breath washout measurements in a pediatric cystic fibrosis outpatient setting. *Pediatric pulmonology.* Aug 2013;48(8):739-746.
18. Nyilas S, Baumeler L, Tamm M, et al. Inert gas washout in bronchiolitis obliterans following hematopoietic cell transplantation. *Chest.* Dec 21 2017.
19. Turner CD, Rey-Casserly C, Liptak CC, Chordas C. Late effects of therapy for pediatric brain tumor survivors. *Journal of child neurology.* Nov 2009;24(11):1455-1463.
20. Schindler M, Belle FN, Grotzer MA, von der Weid NX, Kuehni CE, Swiss Paediatric Oncology G. Childhood cancer survival in Switzerland (1976-2013): Time-trends and predictors. *International journal of cancer. Journal international du cancer.* Jan 01 2017;140(1):62-74.
21. Zorzi AP, Yang CL, Dell S, Nathan PC. Bleomycin-associated Lung Toxicity in Childhood Cancer Survivors. *Journal of pediatric hematology/oncology.* Nov 2015;37(8):e447-452.
22. De A, Guryev I, LaRiviere A, et al. Pulmonary function abnormalities in childhood cancer survivors treated with bleomycin. *Pediatric blood & cancer.* Sep 2014;61(9):1679-1684.
23. Michel G, Gianinazzi ME, Vetsch J, et al. Physicians' experience with follow-up care of childhood cancer survivors - challenges and needs. *Swiss medical weekly.* Jul 19 2017;147:w14457.
24. Kremer LC, Mulder RL, Oeffinger KC, et al. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatric blood & cancer.* Apr 2013;60(4):543-549.

Legends

Table 1 Characteristics of childhood cancer survivors

Table 2 Types of pulmonary function test performed in the first five years after pulmotoxic treatment

Table 3 Predictors for having a pulmonary function test in the first 5 years after pulmotoxic treatment, results from multivariable logistic regression analysis

Figure 1 Proportion and 95% confidence interval of survivors exposed pulmotoxic treatment with pulmonary function tests by Swiss pediatric oncology center (SPOG)

Figure 2 Cumulative incidence of the first plethysmography and/or spirometry in childhood cancer survivors during follow-up stratified by period of cancer diagnosis. Start of follow-up time was the time of the first pulmotoxic treatment.

Supplementary Material

Supplementary Table A1 Recommendations for surveillance of pulmonary dysfunction in international follow-up care guidelines and treatment protocols

Supplementary Table S2 Type of pulmonary disease diagnosis found in medical records, survivors can have more than one pulmonary disease

Supplementary Table S3 Proportion and 95% confidence interval of survivors with pulmonary function tests by Swiss pediatric oncology center

Supplementary Table S4. Predictors for having a pulmonary function test in the first 5 years after pulmotoxic treatment, results from univariable logistic regression analysis

Supplementary Table S5 Pulmonary toxic childhood cancer treatment of CNS tumor survivors

Supplementary Figure S1 Flow chart of study population

Table 1 Characteristics of childhood cancer survivors

	Survivors N = 372	
	n	(%) [a]
Sex		
Male	219	(59)
Female	153	(41)
Age at diagnosis in years		
Median (range)	10.2	(0.3–15.9)
0–4	67	(18)
5–9	111	(30)
10–15	194	(52)
Age at data collection in years[b]		
Median (range)	23.4	(6.2–40.7)
6–14	67	(18)
15–24	152	(41)
≥ 25	153	(41)
Time since cancer diagnosis in years		
Median (range)	13.2	(2.0–25.9)
2–9	139	(37)
10–19	156	(42)
≥ 20	77	(21)
Period of cancer diagnosis		
1990–1997	130	(35)
1998–2005	144	(39)
2006–2013	98	(26)
Diagnosis (ICCC-3)		
I Leukemia	46	(12)
II Lymphoma	131	(35)
IIa Hodgkin's lymphoma	120	(32)
IIb&c Non–Hodgkin's lymphoma	11	(3)
III CNS tumor	107	(29)
IV–XII all other tumors	88	(24)
Relapse		
Yes, one relapse	71	(19)
Yes, two or more relapses	46	(12)
Death during follow-up [c]	57	(15)
Lung-toxic chemotherapy	147	(40)
Busulfan	24	(6)
Nitrosoureas (CCNU/BCNU)	70	(19)
Bleomycin	57	(15)

Table 1 *continued*

Chest radiotherapy, cumulative Gy	323	(87)
1–19	116	(31)
≥ 20	197	(53)
Dose unknown	10	(3)
Thoracic surgery	34	(9)
Hematopoietic stem cell transplantation	87	(24)
Autologous	47	(13)
Allogeneic	40	(11)
Clinical study participation		
Registered as clinical study participant	217	(58)
Treated according to clinical study protocol	124	(34)
Treated not according to clinical study	31	(8)

Abbreviations: CNS, central nervous system; Gy, Gray; ICCC3, International Classification of Childhood Cancer, version 3; IQR, interquartile range

[a] Column percentages are given
[b] Time from pulmotoxic treatment to start of study or date of death
[c] Death during the whole time observed.
[d] Including radiotherapy to the total body, mantle-field, thorax, lungs, mediastinum or thoracic spine.

Table 2 Types of pulmonary function test performed in the first five years after pulmotoxic treatment

	Survivors with pulmonary function test		Number of specific pulmonary function tests in survivors with at least 1 specific pulmonary function test		
(N=372)	N	(%) [a]	Median	IQR	Range
Tests specifically recommended in follow-up care guidelines					
Plethysmography and/or spirometry	185	(50)	3	(2–5)	(1–11)
Plethysmography and spirometry	172	(46)	3	(2–5)	(1–11)
Spirometry only	12	(3)	1	(1–1)	(1–2)
Plethysmography only	1	(<1)	1	(1–1)	(1–1)
Diffusion capacity of carbon monoxide	122	(33)	3	(2–4)	(1–8)
Other tests:					
Bronchodilator test	31	(8)	1	(1–3)	(1–6)
Cardiopulmonary exercise test	11	(3)	1	(1–2)	(1–2)
Exhaled nitric oxide	7	(2)	1	(1–2)	(1–5)
Bronchial challenge test	3	(1)	1	(1–2)	(1–2)
Multiple breath inert gas washout	2	(1)	1.5	(1–2)	(1–2)

Abbreviations: IQR, interquartile range

[a] Row percentages are given

Table 3 Predictors for having a pulmonary function test in the first 5 years after pulmotoxic treatment, results from multivariable logistic regression analysis

		Plethysmography and / or spirometry				DLCO			
		≥ 1 PFT				≥ 1 PFT			
	N=372	n	(%)[a]	OR_{adj}	P [b] (95% CI)	n	(%)[a]	OR_{adj}	P [b] (95% CI)
Overall	372	185	(50)			122	(33)		
Sex					0.543				0.748
Male	219	105	(48)	1.0		70	(32)	1.0	
Female	70	80	(52)	1.2	(0.7–1.9)	52	(34)	0.9	(0.6–1.5)
Age at diagnosis (years)					0.591				0.331
0–4	67	26	(39)	1.0		13	(19)	1.0	
5–9	111	47	(42)	1.5	(0.7–3.2)	30	(27)	1.7	(0.8–3.8)
10–15	194	112	(58)	1.3	(0.6–2.6)	79	(41)	1.7	(0.8–3.8)
Diagnosis (ICCC-3)					<0.001				<0.001
I Leukemia	46	20	(43)	1.0		10	(22)	1.0	
II Lymphoma	131	100	(76)	5.9	(2.2–16.1)	67	(51)	3.4	(1.2–9.5)
IIa Hodgkin's lymphoma	120	94	(78)			61	(51)		
IIb&c Non–Hodgkin's lymphoma	11	6	(55)			6	(55)		
III CNS tumor	107	22	(21)	0.3	(0.1–1.0)	16	(15)	0.5	(0.1–1.5)
IV–XII all other tumors	88	43	(49)	1.2	(0.5–3.2)	29	(33)	1.8	(0.6–5.0)
Period of cancer diagnosis					0.441				0.100
1990–1997	130	63	(48)	1.0		40	(31)	1.0	
1998–2005	144	77	(53)	1.5	(0.8–2.7)	55	(38)	1.7	(0.9–3.0)
2006–2013	98	45	(46)	1.2	(0.6–2.4)	27	(28)	1.0	(0.5–2.4)

Table 3 *continued*

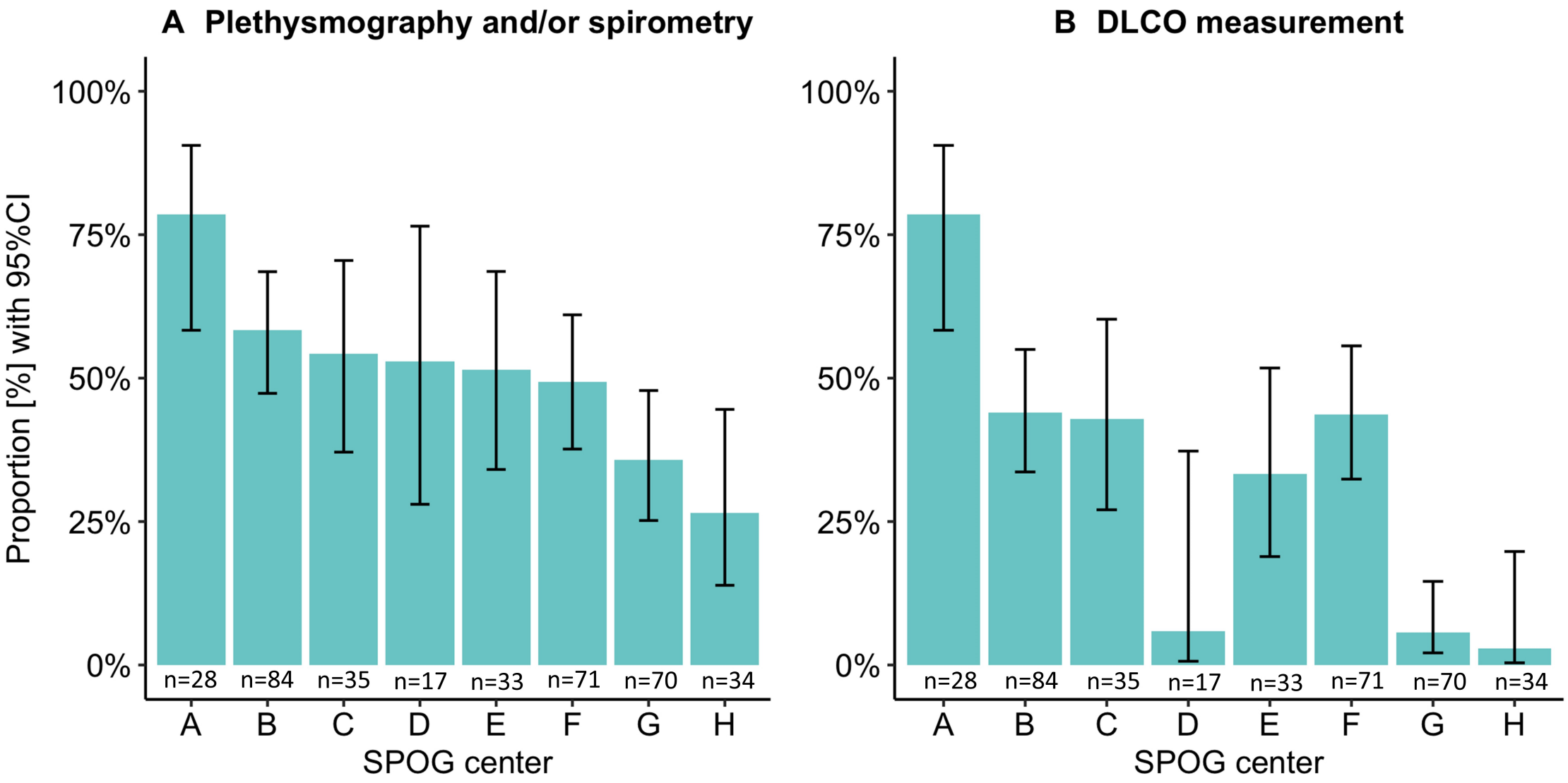
Pulmotoxic treatment					0.408				0.278
Chest radiotherapy	225	113	(50)	1.0		72	(32)	1.0	
Pulmotoxic chemotherapy	48	24	(50)	1.6	(0.8–3.4)	14	(29)	1.1	(0.5–2.4)
Both	99	48	(48)	1.3	(0.7–2.5)	36	(36)	1.7	(0.9–3.0)
Thoracic surgery					0.237				0.852
No	338	165	(49)	1.0		110	(33)	1.0	
Yes	34	20	(59)	1.8	(0.7–4.9)	12	(35)	0.9	(0.4–2.3)
Hematopoietic stem cell transplantation					0.407				0.861
No	285	141	(49)	1.0		97	(34)	1.0	
Yes	87	44	(51)	1.4	(0.6–2.9)	25	(29)	0.9	(0.4–2.0)
autologous	47	24	(51)			15	(32)		
allogeneic	40	20	(50)			10	(25)		
Clinical study participation					0.010				0.082
Registered as clinical study participant	217	113	(52)	1.0		69	(32)	1.0	
Treated according to clinical study protocol	124	65	(52)	1.5	(0.9–2.7)	46	(37)	1.8	(1.0–3.2)
Treated not according to clinical study	31	7	(23)	0.3	(0.1–0.9)	7	(23)	0.9	(0.3–2.5)
Ever had a pulmonary disease/infection					<0.001				0.072
No	300	137	(46)	1.0		92	(31)	1.0	
Noninfectious pulmonary disease	47	38	(81)	8.7	(3.4–22.4)	22	(47)	2.3	(1.1–4.5)
Pulmonary infection	25	10	(40)	0.7	(0.3–1.9)	8	(32)	1.3	(0.5–3.4)
Died during follow-up					0.709				0.969
No	315	165	(52)	1.0		107	(34)	1.0	
Yes	57	20	(35)	0.9	(0.4–1.9)	15	(26)	1.0	(0.5–2.2)

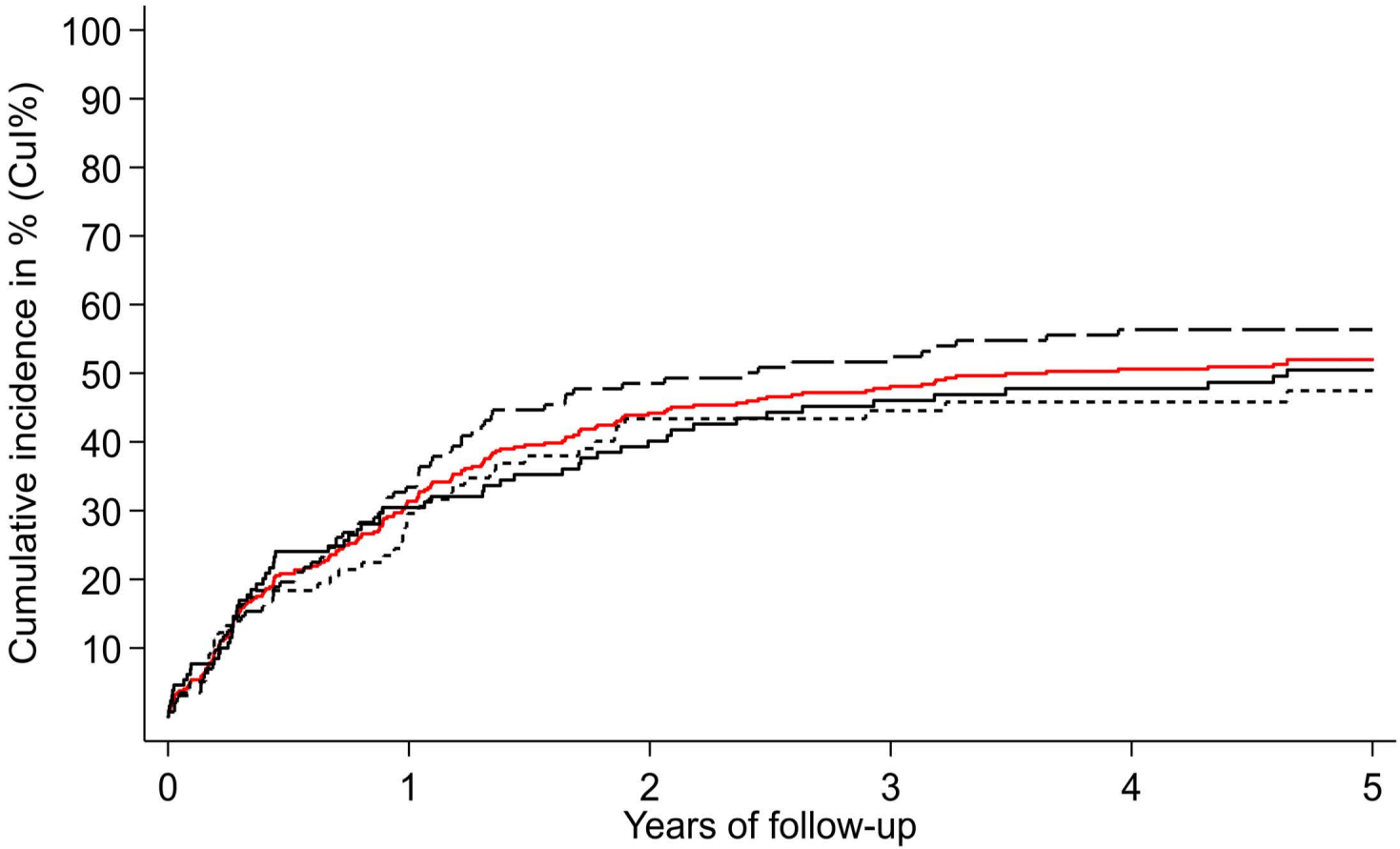
Table 3 *continued*

Abbreviations: CI, confidence interval; CNS, central nervous system, DLCO, diffusion capacity of the lungs for carbon monoxide; ICCC3, international classification of childhood cancer, version 3; OR, odds ratio; PFT, pulmonary function test

[a] Row percentages given.

[b] P-values calculated from global likelihood ratio tests


A Plethysmography and/or spirometry
B DLCO measurement
Proportion [%] with 95%CI
100%
75%
50%
25%
0%
n=28
n=84
n=35
n=17
n=33
n=71
n=70
n=34
A
B
C
D
E
F
G
H
SPOG center



All periods	N (CuI%): 372	247 (31%)	192 (44%)	172 (48%)	151 (51%)	135 (52%)
1990-1997	N (CuI%): 130	88 (30%)	74 (40%)	64 (46%)	60 (48%)	54 (50%)
1998-2005	N (CuI%): 144	90 (33%)	66 (49%)	61 (53%)	55 (56%)	52 (56%)
2006-2013	N (CuI%): 98	69 (31%)	52 (43%)	47 (45%)	36 (46%)	29 (47%)

Supporting information

Journal: Pediatric Blood & Cancer

Monitoring pulmonary health in Swiss childhood cancer survivors

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Supplementary Table S1 Recommendations for surveillance of pulmonary dysfunction in international follow-up care guidelines and treatment protocols

Guidelines			
	Exposure	**Recommended evaluation**	**Timing**
Children's Cancer Study Group (Late Effects Group) Long Term Follow-up Guidelines [1] Therapy based long term follow-up: practice statement UK, 2nd edition, April 2002 1st edition 1995	**Alkylating agents** - Busulfan - Carmustine - Lomustine **Bleomycin** **Chest radiotherapy (including spine)** **Thoracic surgery** **HSCT (with or without cGvHD)**	Pulmonary function test, no further specification	At end of treatment and if symptomatic or abnormal (<2SD below normal), repeat PFT after 1 year.
Children's Oncology Group–Long-Term Follow-Up Guidelines [2] USA, Version 4.0, October 2013 1st edition: 2003	**Alkylating agents** - Busulfan - Carmustine - Lomustine **Bleomycin** **Chest radiotherapy (excluding spine)** **Thoracic surgery** **HSCT with chronic graft versus host disease (cGvHD)**	Pulmonary function test (including DLCO and spirometry)	Baseline at entry in follow-up care, defined as two or more years after completion of therapy. Repeat as clinically indicated.

(Supplementary Table S1 continued)

Treatment Protocols					
	Cancer diagnosis	**N[a]**	**Possible Exposure**	**Recommended evaluation**	**Timing**
GPOH-HD 95	Hodgkin Lymphoma	41	**Chest radiotherapy**	Pulmonary function tests, no further specification	At the end of treatment and then in year 1 and 2 every 6 months, in year 3 and 4 every year, year 5 to 10 if clinically indicated
HIT-2000	Medulloblastoma, supratentorial primitive neuroectodermal tumor, or ependymoma	34	**Craniospinal radiotherapy** **Lomustine**	-	**-**
SPOG H85/87/92	Hodgkin Lymphoma	30	**Chest radiotherapy of the chest** **Bleomycin**	Pulmonary function tests, no further specification	1 year after end of therapy if abnormal repeat annually, or for 5 years
Euro-E.W.I.N.G 99	Ewing Sarcoma	14	**Chest radiotherapy** **Busulfan**	Minimum: clinical examination Pulmonary function tests (including DLCO)	At end of treatment and if abnormal repeat yearly, if normal repeat 5 yearly and at the end of puberty
GPOH-HD Pilot 2002	Hodgkin Lymphoma	14	**Chest radiotherapy**	Pulmonary function tests, no further specification	1, 2, and 5 years after end of therapy, in between if clinically indicated
POG A9961	Average risk Medulloblastoma	10	**Craniospinal radiotherapy** **Lomustine**	Pulmonary function tests (lung volumes, spirometry and DLCO)	Pretreatment, at end of therapy, 1, 3 and 5 years after the end of therapy
COG ACNS0331	Standard risk Medulloblastoma	8	**Craniospinal radiotherapy** **Lomustine**	-	**-**

(Supplementary Table S1 continued)

POG 9031	Advanced Medulloblastoma	8	**Craniospinal radiotherapy**	Late effects evaluation, list of available complications criteria includes vital capacity, DLCO	-
EURONet-PHL-C1	Hodgkin Lymphoma	7	**Involved field radiotherapy** **Bleomycin (with relapse)** **Carmustine (with relapse)**	Pulmonary function tests, no further specification	6 weeks after end of treatment, afterwards as clinically indicated
EWOG-MDS 98	Myelodysplastic syndrome	7	**Busulfan**	-	-
ALL SZT BFM 2003	Acute lymphoblastic leukemia	6	**Total body irradiation** **Busulfan**	Pulmonary function tests, no further specification	At end of treatment, after 6 month, 1, 2 and 4 years
HIT 91	Medulloblastoma, supratentorial primitive neuroectodermal tumor, or ependymoma	6	**Craniospinal radiotherapy** **Lomustine**	-	-
POG 9049	High risk malignant germ cell tumors	6	**Bleomycin**	Pulmonary function tests, no further specification	Optimal prior to each course of chemotherapy, after induction and after maintenance, 2 and 5 years after end of treatment

Abbreviations: DLCO, Diffusion capacity of the lung for carbon monoxide; FVC, Forced vital capacity; FV, Flow volume; HSCT, hematopoietic stem cell transplantation; SD, Standard deviation; TLC, Total lung capacity

[a] Number of children in our study treated with said protocol. 90 other study protocols were used in our study, but each in five or less children.

References:

[1] Therapy based long-term follow-up: practice statement 2nd edition, April 2005, 2005. https://www.uhb.nhs.uk/Downloads/pdf/CancerPbTherapyBasedLongTermFollowUp.pdf. Accessed 10 Nov 2017.
[2] COG Long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancer, version 4.0–October 2013. 2013. http://www.survivorshipguidelines.org/. Accessed 10.11.2017.

Supplementary Table S2 Type of pulmonary disease diagnosis found in medical records, survivors can have more than one pulmonary disease

	Survivors (N=372)	
	N	(%) [a]
Ever had a pulmonary disease diagnosis [b]	72	(20)
Noninfectious pulmonary diseases [c]	47	(13)
Pulmonary infections	25	(7)
Noninfectious pulmonary diseases:		
Asthma	19	(5)
Diffuse parenchymal lung disease:	22	(6)
Restrictive lung disease	20	(5)
Interstitial lung disease	5	(1)
Bronchiolitis obliterans	1	(<1)
Atelectasis	3	(1)
Chest wall deformity	2	(1)
Emphysema	1	(<1)
ARDS [d]	7	(2)
Pulmonary Infections: [e]		
Pneumonia (viral, bacterial)	30	(8)
Aspergillosis	5	(1)

[a] Column percentages given
[b] This includes all pulmonary disease diagnoses, which were present after the cancer diagnosis, regardless if the pulmonary disease was diagnosed before or after the cancer diagnosis.
[c] If survivors had any of the following diseases they were categorized as pulmonary diseases: restrictive lung disease, asthma, interstitial lung disease, atelectasis, chest wall deformity, emphysema, bronchiolitis obliterans. If they had both pulmonary disease and pulmonary infection they were categorized into pulmonary diseases.
[d] If survivors had ARDS because of a pulmonary infection they were categorized as pulmonary infections only; if they had ARDS because of acute treatment-related side effects and another pulmonary disease they were categorized as pulmonary diseases, and if they had ARDS only because of acute treatment related side effects, they were categorized to no pulmonary disease diagnosis.
[e] Of 35 survivors with pulmonary infections 10 had additional noninfectious pulmonary diseases and were coded to noninfectious pulmonary diseases for further analysis.

Supplementary Table S3 Proportion of pulmonary function tests by Swiss pediatric oncology center

		Plethysmography and/or spirometry			DLCO		
	N=372	n	(%) [a]	(95% CI)	n	(%) [a]	(95% CI)
Center [b]							
A	28	22	(79)	(58–91)	22	(79)	(58–91)
B	84	49	(58)	(47–69)	37	(44)	(34–55)
C	35	19	(54)	(37–71)	15	(43)	(27–60)
D	17	9	(53)	(28–76)	1	(6)	(1–37)
E	33	17	(52)	(34–69)	11	(33)	(33–91)
F	71	35	(49)	(38–61)	31	(43)	(32–56)
G	70	25	(36)	(25–48)	4	(6)	(2–15)
H	34	9	(26)	(14–45)	1	(3)	(0–20)

Abbreviations: DLCO, Diffusion capacity of the lungs for carbon monoxide
[a] Row percentages are given
[b] Centers are anonymized

Supplementary Table S4. Predictors for having a pulmonary function test in the first 5 years after pulmotoxic treatment, results from univariable logistic regression analysis

		Plethysmography and/or spirometry				**DLCO**			
		≥ 1 PFT				≥ 1 PFT			
	N=372	n	(%)[a]	OR_{adj}	P [b] (95% CI)	n	(%)[a]	OR_{adj}	P [b] (95% CI)
Overall	372	185	(50)			122	(33)		
Sex					0.410				0.683
Male	219	105	(48)	1.0		70	(32)	1.0	
Female	153	80	(52)	1.2	(0.7–1.8)	52	(34)	1.1	(0.7–1.7)
Age at diagnosis (years)					**0.005**				**0.002**
0–4	67	26	(39)	1.0		13	(19)	1.0	
5–9	111	47	(42)	1.2	(0.6–2.2)	30	(27)	1.5	(0.7–3.2)
10–15	194	112	(58)	2.2	(1.2–3.8)	79	(41)	2.9	(1.5–5.6)
Diagnosis (ICCC-3)					**<0.001**				**<0.001**
I Leukemia	46	20	(43)	1.0		10	(22)	1.0	
II Lymphoma	131	100	(76)	4.2	(2.1–8.5)	67	(51)	3.8	(1.7–8.2)
IIa Hodgkin's lymphoma	120	94	(78)			61	(51)		
IIb&c Non–Hodgkin's lymphoma	11	6	(55)			6	(55)		
III CNS tumor	107	22	(21)	0.3	(0.2–0.7)	16	(15)	0.6	(0.3–1.5)
IV–XII all other tumors	88	43	(49)	1.2	(0.6–2.5)	29	(33)	1.8	(0.8–4.1)
Period of cancer diagnosis					0.482				0.186
1990–1997	130	63	(48)	1.0		40	(31)	1.0	
1998–2005	144	77	(53)	1.2	(0.8–2.0)	55	(38)	1.4	(0.8–2.3)
2006–2013	98	45	(46)	0.9	(0.5–1.5)	27	(28)	0.9	(0.5–1.5)

(Supplementary Table S4 continued)

Pulmotoxic treatment					0.959				0.631
Chest radiotherapy only	225	113	(50)	1.0		72	(32)	1.0	
Pulmotoxic chemotherapy only	48	24	(50)	1.0	(0.5–1.8)	14	(29)	0.9	(0.4–1.7)
Both	99	48	(48)	0.9	(0.6–1.5)	36	(36)	1.2	(0.7–2.0)
Thoracic surgery					0.265				0.746
No	338	165	(49)	1.0		110	(33)	1.0	
Yes	34	20	(59)	1.5	(0.7–3.1)	12	(35)	1.1	(0.5–2.4)
Hematopoietic stem cell transplantation					0.857				0.353
No	285	141	(49)	1.0		97	(34)	1.0	
Yes	87	44	(51)	1.0	(0.6–1.7)	25	(29)	0.8	(0.5–1.3)
autologous	47	24	(51)			15	(32)		
allogeneic	40	20	(50)			10	(25)		
Clinical study participation					**0.005**				0.261
Registered as clinical study participant	217	113	(52)	1.0		69	(32)	1.0	
Treated according to clinical study protocol	124	65	(52)	1.0	(0.7–1.6)	46	(37)	1.3	(0.8–2.0)
Treated not according to clinical study	31	7	(23)	0.3	(0.1–0.6)	7	(23)	0.6	(0.3–1.5)
Ever had a pulmonary disease/infection					**<0.001**				0.077
No	299	136	(45)	1.0		92	(31)	1.0	
Noninfectious pulmonary disease	51	41	(80)	5.5	(2.6–12.5)	24	(47)	2.1	(1.1–3.8)
Pulmonary infection	22	8	(36)	0.6	(0.3–1.7)	6	(27)	0.8	(0.3–2.1)
Died during follow-up					**0.016**				0.250
No	315	165	(52)	1.0		107	(34)	1.0	
Yes	57	20	(35)	0.5	(0.3–0.9)	15	(26)	0.7	(0.4–1.3)

Abbreviations: CI, confidence interval; CNS, central nervous system; DLCO, diffusion capacity of the lungs for carbon monoxide; ICCC3, international classification of childhood cancer, version 3; OR, odds ratio; PFT, pulmonary function test

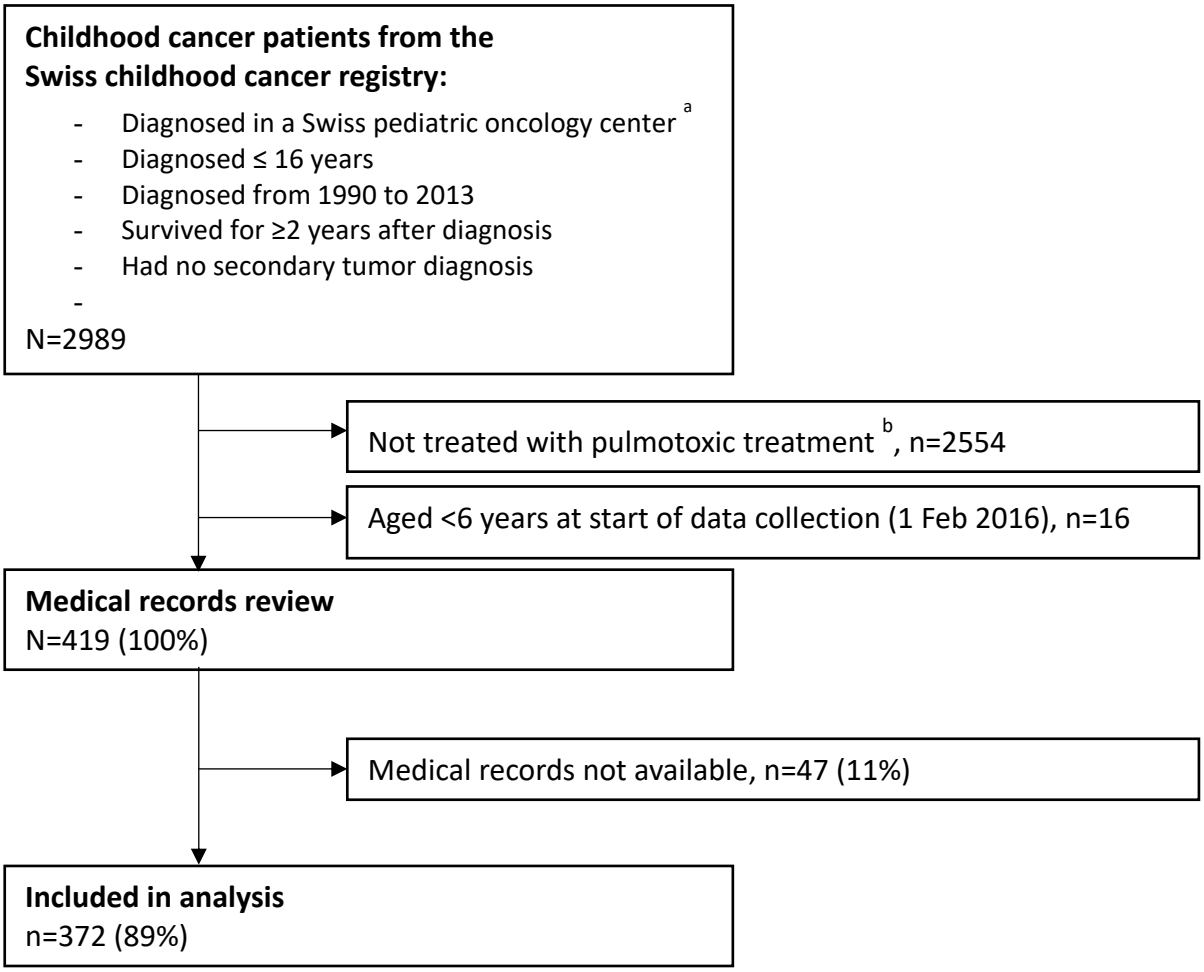
[a] Row percentages given.

[b] P-values calculated from global likelihood ratio tests.

Supplementary Table S5 Pulmonary toxic childhood cancer treatment of CNS tumor survivors

	Survivors of CNS tumors N = 107	
	n	(%) [a]
Lung-toxic chemotherapy	63	(59)
Nitrosoureas (CCNU/BCNU)	63	(59)
Chest radiotherapy [a], cumulative Gy	95	(89)
1–19	1	(1)
≥ 20	92	(86)
Dose unknown	2	(2)

Abbreviations: CNS, central nervous system; Gy, Gray;
[a] Included fields: thoracic spine (n=94), total body irradiation (n=1)



Supplementary Figure S1 Flow chart of study population

[a] Including the following centers with pediatric oncology units: Kinderklinik Kantonsspital Aarau AG, Universitäts-Kinderspital Basel, Universitäts-Kinderklinik Inselspital Bern, Hospital des Enfants Geneve, CHUV Lausanne, Kinderklinik Kantonsspital Luzern, Ostschweizer Kinderspital St. Gallen, Universitäts-Kinderspital Zürich
[b] Pulmotoxic treatment defined as chemotherapy with busulfan, bleomycin, lomustine or carmustine and/or chest radiotherapy